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MICROFLUIDIC OPERATIONS AND NETWORK ARCHITECTURE CHARACTERIZATIONS (MONARCH) PROJECT

Duke University

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1. Program Goals

Duke University in partnership with Becton Dickinson Corp. has performed a research effort to design and evaluate architecture for a reconfigurable microliquid handling system with biomedical applications. The design aspect has leveraged and has integrated component-level technology concerning micropumps, valves, reservoirs, channels, sensors, and fluidic logic elements to develop a microliquid handling system that could be reconfigured and reused for a variety of applications. The evaluation aspect has targeted the construction of a robust, hierarchical analysis capability encompassing both architectural system simulation with functional macro modeling and circuit component simulation using lumped-parameter nodal modeling. While the original goal was to use VHDL-AMS in addressing both discrete and continuous time extensions in hierarchical simulation, further work showed that this hardware description language was less suitable than the System C language. Finally, a critical aspect of the work performed has been physical implementation concerning substrate integration. The use of standard continuous flow components seriously limits microfluidic system scaling. To overcome this limitation, a new microfluidic's technology was invented based upon voltage control for the actuation of discrete droplets of fluids. This technology was successfully demonstrated, and subsequent efforts in MONARCH have been directed toward system design, simulation, and fabrication using droplet-based digital microfluidics.

The MONARCH program pursued an aggressive set of research objectives, balanced by an associated set of technology demonstrations and pilots to assess progress, determine future directions, and ensure successful results. This strategy provided the coordinating organization and focus to develop the following set of project deliverables, generally combined under the heading of Task 1.0: MONARCH Technology Development:

- Reconfigurable microliquid handling system architecture specification defining constituent components and their interfaces for composing microfluidic systems supporting a broad range of biomedical applications.
- Reconfigurable microliquid handling system architecture simulation and design driver pilots respectively demonstrating salient system operation/performance of biomedical applications and showing actual fabrication feasibility for critical components.
- Process flow performance and stochastic simulation built on top of discrete-event simulation, thus demonstrating the applicability of a hierarchical language to serve as a system design language for both continuous and discrete processes.
- Microfluidic component circuit modeling and simulation built on top of VHDL-AMS simulation demonstrating a unified composite CAD intellectual property strategy and technology.

- Technology-specific model parameterization and estimation to respectively accommodate rapidly advancing microfluidic technologies and analysis of partial microfluidic system design information.
- Microfluidic system intelligent substrate specification and design driver pilots to establish new foundry interoperability interfaces enabling a technology strategy for easily assembling a diverse collection of microfluidic components and sensors into a reconfigurable microliquid handling system.

A second general task was Task 2.0: MONARCH Technology Demonstration. This task included architectural design, modeling and simulation, and pilot fabrications. The third task was Task 3.0: MONARCH technology Transition. In the sections below, progress in each of the above tasks is summarized and a detailed report is then attached after each section as an appendix to provide complete information.

2. TASK 1.0: MONARCH Technology Development

- Task1.1 Reconfigurable Microliquid Handling System Architecture

- TASK 1.1.1: Bio-fluidic Applications Analysis

Goals:

1. Identify a general biomedical application set and specific applications to be used by MONARCH. Identify a common set of constituent elemental operations aligned with reconfigurable microfluidic architectural processing operations.
2. Define process flow simulation of biomedical applications and illustrate composition of elemental operations into processes via protocols.
3. Define process flow and architectural (performance) simulation of biomedical applications. Show hierarchical model/simulation decomposition and salient transport and reactions.

Results:

This task has been focused on identifying the general biomedical application set and the specific applications to be used by the MONARCH reconfigurable architecture as well as architectural design and analysis. We have focused primarily on continuous flow fluidic systems. However, the complexity of physically implementing anything but sequential process flow systems is enormous. As a result, we exploited the significant advantages of droplet-flow technology in our biomedical applications research. For example we have looked at the development of a reconfigurable bio-molecular detection microsystem architecture composed of an array of droplet-actuation and detection sites in a decision

tree with reconfigurable pipelines for molecular recognition using parallel, high-speed droplet transport. This architecture is based on a collection of detection criteria allowing a decision flow path to be programmed into the system by a set of decision rules. At each detector site the unknown chemistry within the droplet will accumulate "bits" until sufficient bits exist to make identification. The key to this type of architecture is molecular recognition technology in which multiple simple tests can substitute for single, time-consuming but highly selective tests. Work continued to identify these types of simple tests in conjunction with bioanalytical chemists and biophysicists. Work was completed on a demonstration of forming DNA microspots on derivatized glass using dynamic stamping of DNA-containing droplets, PCR. Work that was not completed under MONARCH was the demonstration of an on-chip 1:n dilution mixer, a single-chip reconfigurable microdialysis system, and a fluidics-based optical switch.

A detailed discussion of the biomedical applications analysis and initial results obtained in process flow simulation are presented in the work by Jason Jopling: "Microfluidic Architecture and Biomedical Applications and Simulation", M.S. Thesis, May 1, 2000.

Future Work:

Additional work that needs to be performed in this area is identified below:

Task 1.1.1 goals for future work:

1. Identify droplet-based architectures for the following applications: DNA synthesis of microarrays; polymerase chain reactions (PCR); 1:n dilution mixer; reconfigurable micro-dialysis system; microfluidic-based optical switch.
2. Develop architecture/structure for these applications by simulation and experiment.
3. Integrate architectural simulation with component-level simulation of droplet transport, mixing, and analyte detection.
4. Develop reduced-order models for optical detection processes in enzyme-based biosensors, and obtain scaling rules. Use these models and scaling rules to design and optimize optical detection systems for droplet-based architectures. Also use models in a high-level simulation environment.
5. Transition droplet-based system architectures for commercial exploitation.

- TASK 1.1.2: Architecture Design and Analysis

Goals:

1. Investigate basic control and power design issues for the reconfigurable microliquid handling system architecture.
2. Design base line reconfigurable microliquid handling system architecture to support elemental biomedical operations. Show operation via architectural simulation.

3. Refine reconfigurable microliquid handling system architecture and show operation via simulation. Show hierarchical links to higher-level process flow simulation and lower-level component nodal simulation.

Results:

Work has focused on the use of System C, rather than VHDL-AMS, as a modeling language for hierarchical MEFS simulation. System C, which extends the capabilities and advantages of C/C++ into the hardware domains, has been proposed as the new version of the next-generation design platform. System C is a C++ class library and a methodology that can be used to effectively create a cycle-accurate model of software algorithms, hardware architectures, and interfaces of SoC (System On a Chip) and system-level design. Depending on the characteristics of each simulation language, and modeling and simulation requirements for MEFS design, we compared among different simulation languages. Based on these comparisons, we selected System C as a potential candidate. Then, an integrated modeling and simulation environment for MEFS can be built with System C.

System-level modeling of MEFS using a hierarchical System C environment has now been demonstrated. We have developed a MEFS CAD closed-loop integration strategy along the lines of microelectronics CAD. This strategy extends system design from the component level to the systems level, and includes hierarchical modeling, a hierarchical design environment, hierarchical performance evaluation, and hierarchical optimization. Preliminary architectural simulations have been performed, whereby MEFS architectural concepts can be compared. A full description of this work is described in the work by T. Zhang: "An Integrated Hierarchical Modeling and Simulation Approach for Microelectrofluidic Systems," Ph.D. Thesis, May, 2001.

Hierarchical modeling and simulation has been demonstrated by comparing a reconfigurable continuous-flow PCR architecture with a droplet-based PCR architecture. The continuous flow system needed a total of 10 three-way valves and six actuation micropumps with flow sensors. The projected size was 700 square mm, and the system processing capability at high traffic rates saturated at about 7 samples/hour. By contrast, an equivalent reconfigurable droplet PCR architecture could be implemented in a fraction of the size and does not require any MEMS components. System processing capability at high traffic rates saturated at about 14 samples/hour. Thus, we have demonstrated that the droplet-based PCR system provides higher performance as well as lower design and integration complexity.

Definition of MONARCH architecture moved away from the use of continuous flow components and towards the use of electrowetting technology once initial demonstrations of the technology were made. The first detailed architectural study of MONARCH V2.0 architecture was completed in May, 2000. This work focused on the particular optimization issues of V2.0, using integer linear programming methods to minimize the latency of the analytical tasks. A detailed discussion of "digital microfluidic" architecture

described in the work by J. Ding: “System Level Architectural Optimization of Semi-reconfigurable Microfluidic System,” M.S. Thesis, April, 2000.

Future Work:

Continuation of hierarchical system design and analysis needs to be extended to droplet-based architectures with the following goals and deliverables:

Task 1.1.2 goals for future work:

1. Develop a droplet-based application platform within the current hierarchical design environment. This work will be driven by the efforts in Task 1.1.1.
2. Develop a strategy for linking ODAE models with ODAE solvers within the System C environment
3. Implement multi-step optimization methods to assure global optimization results.
4. Verify models for specific applications about their design space.
5. Make System C design system available to the MEFS community

- TASK 1.2: Architectural System Simulation

- TASK 1.2.1: Process Flow System Simulation

Goals:

1. Survey process flow simulation technology and representative commercial simulation packages supporting modeling and analysis of biomedical applications. Identify commercial simulation packages for possible initial use. Conduct pilot biomedical application comparative modeling and analysis using VHDL and higher order languages.
2. Support process flow simulation of biomedical application analysis. Define initial modeling methodology and associated set of VHDL packages for process flow simulation.
3. Refine modeling methodology for process flow simulation of biomedical applications.

Results:

This work has been completed as part of Task 1.1.2, and is described in detail in the work of T. Zhang: “An Integrated Hierarchical Modeling and Simulation Approach for Microelectrofluidic Systems,” Ph.D. Thesis, May, 2001.

- TASK 1.2.2: Stochastic Architectural Simulation

Goals:

1. Survey performance simulation technology and commercial packages supporting modeling and analysis of biomedical applications. Define requirements and applicability of VHDL standards.
2. Support architectural simulation of biomedical application analysis. Define initial modeling methodology for stochastic (performance) simulation of applications.
3. Refine modeling methodology for performance simulation of applications. Define hierarchical links to high and lower levels.

This work has been completed as part of Task 1.1.2, and is described in detail in the work of T. Zhang: “An Integrated Hierarchical Modeling and Simulation Approach for Microelectrofluidic Systems,” Ph.D. Thesis, May, 2001.

- TASK 1.3: System and Circuit Component Simulation

Goals:

1. Study design of microfluidic pumps and valves involving a variety of actuation techniques and flow rates. Select a set of microfluidic pumps and valves to model in detail. Identify differential and algebraic equations governing physical behavior.
2. Cast microfluidic pump and valve differential and algebraic equations into simulation models using both MAST and VHDL-AMS. Show simulation behavior.
3. Interface circuit component simulation to higher-level performance simulation. Develop modeling methodology and guidelines and integrate with larger composite CAD, mixed signal VHDL-AMS modeling and model interoperability efforts.

Results:

We completed building a library of basic MEFS components and showed how these library models could be combined to simulate a micropump. Results have been compared with FEM simulation data, and the results were adequate. We also evaluated generally the use of VHDL-AMS in MEFS modeling. VHDL-AMS allows designers to

model a MEFS system that can be represented by a set of DAEs at any level of abstraction. But the largest limitation on VHDL-AMS modeling is the lack of simulators. Analytical modeling of a MEFS system is not always possible due to the complex geometry and possible field coupling. When the system's geometry becomes complex, finite element analysis may be applied to simulate device behavior. But the result obtained through FEM is a set of numerical data. How to transform the numerical data into a mathematical expression becomes a problem. Because of several key limitations in the use of VHDL-AMS in MEFS component modeling, this effort was closed in 2nd quarter of 2000. However, the results of this study were in fact used in the hierarchical modeling effort of Task 1.2.

Details of this work are described in the work of F. Cao: , “Microfluidic System (MEFS) Component Modeling and Simulation,” M.S. Thesis, April, 2000.

A description of additional work on modeling and simulation is presented under Task 2.2.

- TASK 1.4: Intelligent Substrate

Goals:

1. Define requirements for an intelligent substrate to support the realization of the reconfigurable microliquid handling system architecture using hybrid manufacturing and semicustom design technology.
2. Define initial layout of an intelligent substrate to support baseline reconfigurable microliquid handling system architecture design.
3. Refine layout to support updated reconfigurable microliquid handling system architecture design. Define a manufacturing process for the intelligent substrate.

Results:

- Continuous Flow System

Research related to the Intelligent Substrate was directed to the implementation of an integrated microelectrofluidic system prototype. The Intelligent Substrate Continuous Flow Implementation research effort was focused on fabricating all of the levels of the backbone MONARCH architecture in low-temperature co-fired ceramic tape (LTCC) technology.

Our work was focused in two areas, the first of which was the exploration of the canonical flow geometries postulated in our architectural applications studies. Of the geometries studied, the 90 degree mitered elbow with rectangular cross-section appeared to be the limiting case, and so it served as a convenient basis for comparison. Pressure versus Reynolds number in rectangular cross-section mitered elbows was studied for

various elbow angles (0-90 degrees) and aspect ratios (0.25-parallel plate), in order to provide some insight into the "flow resistance" quantified by head loss (or any other equivalent representation). In this instance, Reynolds number is derived using the hydraulic diameter, an approach that is justified in the literature. Inspection of the resulting flow patterns indicated that flow could be classified as "creeping" at Reynolds numbers below approximately 30-40 in the case of the 90° elbow. This classification refers to flows in which loss is entirely frictional, and the geometry can be accurately modeled by a length of straight channel with centerline length equal to the centerline length of the original geometry. Flows at higher Reynolds numbers begin to exhibit eddy behavior, which introduces inertial losses. Each new eddy forms downstream of any previous eddies, so that a significant portion of the flow structure associated with the elbow exists in the downstream leg, indicating significant exit lengths. At Reynolds numbers on the order of 200-500 the exit length in a 90° mitered elbow exceeds 20 hydraulic diameters. Elbows with smaller angles respond similarly, except that the Reynolds number corresponding to a given exit length tends to increase nonlinearly with decreasing angle. The other geometries studied exhibit similar characteristics in terms of flow complexity vs. Reynolds number, and exit length vs. Reynolds number, although the critical values at which flow is no longer creeping varies from geometry to geometry.

There are several conclusions to be drawn from this work. Very simple straight-channel models are quite accurate for all of the studied geometries, up to Reynolds numbers around 30. The straight-channel models are very inaccurate above this range, but superposition can still be used to model a complicated system as a collection of these canonical elements at Reynolds numbers up to around 100. Above this range, exit lengths become very significant. Since most microscale systems do not provide enough length downstream of any of these canonical geometries for flow to become fully developed at these Reynolds numbers, single-element simulations do not provide accurate insight into system level behavior. In other words, at high Reynolds numbers, the system behaves as a new, single geometry, rather than as a collection of simpler connected geometries.

Our work on the continuous flow substrate also involved the design and implementation of an experimental setup that could be used to evaluate existing prototype and connector assemblies. The setup consisted of several manual syringes, pressure chambers, and pressure gauges. The setup was designed to accommodate pressurizing the unit under test in either of two ways. At low pressures, a pressure chamber can simply be filled with fluid (water) and elevated. The pressure developed at the chamber output (also the test unit input) can be calculated from the chamber elevation, and correlated with the flow rate observed by measuring the amount of effluent collected over a given time interval. At higher pressures, the chamber is partially filled with fluid. An air-filled syringe is connected to the chamber above the water line, and is used to pump air into the chamber, pressurizing the contained fluid. The chamber output is connected to a simple water-column anemometer, and to the test unit input. The anemometer allows direct measurement of the pressure applied to the test unit input, given a fluid with constant density, so compression of the air trapped above the fluid in the pressure chamber does not complicate interpretation of the results. A machining problem delayed the timely

completion of the pressure chambers, so evaluation and experimental results were not completed.

This work was terminated in the third quarter of 2000 due to two things: 1) it became evident that a continuous flow intelligent substrate would not scale. The components were too complex, and even the MONARCH V1.0 architecture could not be implemented; 2) unit flow or droplet technology became the obvious technology choice for MEFS.

- Unit Flow System

A second aspect of the intelligent substrate effort is developing a liquid transport process that lends itself to reconfigurability, programmability, and large dynamic flow rate ranges. We investigated electrowetting as a means of moving droplets of fluid under voltage control.

The unit flow portion of the MONARCH project sought to establish the feasibility of discrete droplet transfer as the basis for a general-purpose microfluidic processing system. Droplet transfer is accomplished through electrically induced surface tension gradients (electrowetting phenomenon). Fabrication and testing of the first prototype actuators was completed in the first quarter 2000, and the concept of fluidic transport of droplets was confirmed.

Having demonstrated reliable transport of electrolyte droplets on 1-D and 2-D microactuator arrays we have sought to gain a better understanding of the factors affecting the speed of droplet transport. We have fabricated and tested structures of various sizes to explore the scaling behavior of the actuation mechanism. We find that the linear velocity of droplet travel as a function of applied voltage is approximately constant over length scales ranging from 1.5 mm to 0.15 mm with associated droplet volumes of 1000 nl to 1 nl. Linear velocities of greater than 10 cm/s can be achieved with voltages less than 100 V when silicone oil is used as a bathing medium. We were thus able to achieve transfer rates in excess of 1000 Hz with a 0.15 mm electrode pitch design.

As part of our effort to develop models of droplet transport we probed the physics underlying electrowetting microactuation and droplet motion. In particular, we conducted fundamental electrowetting studies using our parylene/Teflon insulator system. Capacitance measurements were used as a tool to study both the dynamics of droplet transport and the dynamics of oil/water interactions at the solid/liquid interface. Our results suggested that while silicone oil facilitates droplet transport, it interacts with the aqueous and solid phases in a complex manner. For example, we saw experimentally that the droplet must "squeeze" oil out from beneath during transport. Details of these studies can be found in the work of M.G. Pollack: "Electrowetting-Based Microactuation of Droplets for Digital Microfluidics," Ph.D. Thesis, May, 2001.

We also investigated alternative insulator systems. For example, it has been suggested in the literature that thick Teflon AF films (without parylene) may provide sufficient

dielectric properties for low-voltage electrowetting with reduced process complexity and reduced susceptibility to charging. However, after numerous experimental trials we have found that preparation of high-quality defect-free thick Teflon AF films is very challenging and parylene still appears to offer the best solution. Additionally, we are addressing important device and system level aspects of electrowetting-based systems. We have designed and tested structures for variable ratio droplet mixing and on-chip reagent storage. We also studied issues related to the physical integration of electrowetting chips with optical detection methods.

Initial capacitive studies of electrowetting and droplet transport phenomena were completed. Capacitance measurement of electrowetting electrodes was demonstrated as a sensitive technique for the detection of and determination of droplet position. Static capacitance measurements of resting droplets were also studied in an attempt to link fundamental electrowetting phenomena to observed droplet transport behavior. These studies have yielded insight into the physical processes underlying droplet motion.

We also worked with Nanolytics Inc. to build a unit-flow-based resynthesizable DNA microarray system. Building this device helped us to focus on the important technology issues of the intelligent substrate. The system allowed for rapid bench-top synthesis of DNA assays from a droplet-based system that routes liquids to predetermined array sites. This effort will assist in the technology transition of unit flow microfluidics.

A key aspect of the system relies on "dynamic stamping", whereby a droplet is pulled through a hole in a middle plate electrostatically, and is made to stamp its contents on a receiving glass plate. Fabrication of a system that allows zaxis actuation of DNA-containing droplets has been completed.

It was established by experiment that it is possible to actuate droplets along the z axis using low voltages of 40 volts. Experimental observations were as follows: if the drop is placed on the base plate and a voltage is applied across a middle platinum wire and a top plate, the drop gets pulled up to the top surface almost instantly. Since the top plate is hydrophilic, the droplet surround and confined by oil sticks to the top plate.

Since the end application was to be a DNA microarrayer, it was felt that demonstrating with actual DNA would be necessary. For this a representative DNA strand was chosen and its binding onto glass surfaces determined. The following choices were made:

DNA : Salmon Sperm DNA (Ambion Inc)
Glass: derivatization using poly-l-lysine.

These choices were made after consulting with experts in the genomics center at Duke. The scanned image had a color proportional to the amount (number of nanograms) of DNA present on the spot. This in turn was nothing but volume x concentration. Since concentration was known, we could determine volume spotted from the color intensity. Also, the drop footprint was visible on the top glass plate. It was observed that the derivatized glass surface is fairly hydrophilic. This means that drop spreading is visible.

A model was developed for predicting the minimum voltage that was needed to achieve actuation. At present the model overestimates the experimental value. So, the model was being refined to make more accurate predictions. Part of the work was also directed to determining the relationship between applied voltages and physical geometries. For this purpose center plates with different hole diameters were being made. However, best results were obtained with a platinum wire as the middle electrode. Successful results were obtained in DNA stamping to a spot size of 0.3mm^2 . Details of this work are found in the work of P. Kolar: , “Non-contact Electrostatic Stamping for DNA Microarrays,” M.S. Thesis, August, 2001.

We also have successfully demonstrated the design of a continuous-unit flow buffer. The system was designed as an interface between a continuous-flow system and a unit-flow system. An external pressure source was built to drive continuous liquid flow to the unit flow substrate. The dispensing of droplets of water off of the input pads was controlled by changing the voltage on the pads so as to capture a droplet whose dimensions were controlled by the final pad electrode size and the size of the air gap between the pad and the top ground plane. For a 1.2mm wide electrode path, the generated droplets had a diameter of 1.3-1.4mm over 100 droplets. The result was that reasonably good volume uniformity could be achieved across the number of droplets introduced into the unit flow system. Details of this work are found in the work of J. Wu: “Design and Fabrication of an Input Buffer for a Unit Flow Microfluidic System,” M.S. Thesis, May, 2000.

The unit flow intelligent substrate needs to allow physical and chemical mixing of various constituents. We have demonstrated that under certain conditions, very rapid mixing of the contents of two droplets can be made to occur. Details of drop-to-drop mixing are described in Appendix 9 attached hereto. We also developed a binary architecture that allows 1:n dilution to be achieved, where n is between 1 and 64. This architecture is based on an interpolating, binary A/D converter architecture. This system is being built and will be tested.

Our work this past quarter was spent evaluating and trying various strategies for studying the mixing problem from various sources in the literature and formulating the experimental strategy. The experiments were then performed with fluorescein as the chosen strategy. Work was also performed in analyzing the results, and looking at new ways of visualizing droplet transport and mixing. The progress achieved so far is that we have identified fluorescein marking of the droplets to study mixing. We have data with regard to the electrowetting motivated droplet mixing and plain diffusion mixing of droplets. We are currently experimenting with various dimensions of the gap between top and bottom plate as a larger gap seems to accelerate mixing compared to a smaller gap. A gap height of .2mm produces mixing in four minutes (diffusion), but a gap height of 0.5mm allows mixing in four seconds! We are currently performing more experiments to verify this effect. Also we are quantifying the mixing efficiency with varying frequencies of droplet oscillation over 3 electrodes, and are developing computational models.

Future Work:

Important system-level design issues remain to be investigated for droplet-based devices. These include estimates of power consumption, threshold voltage models, actuation kinetics of different types of fluids, droplet-droplet mixing kinetics, transport models, and the effects of different insulating materials. Each study involves fundamental measurements on test structures with the goal of developing phenomenological models for incorporation in the SSSS system simulator.

Task 1.4 goals for future work:

1. Define fabrication processes and materials for a stable micro-droplet system operation.
2. Implement a prototype architecture and perform characterizations. Refine the layout of the intelligent substrate to support more complex reconfigurable microliquid handling system architecture design.
3. Develop fundamental understanding of droplet/insulator interface to form a basic actuation model.
4. Develop fundamental understanding of droplet-droplet coalescence and mixing, and develop mixing model.

3. TASK 2.0: MONARCH Technology Demonstration

- Task 2.1 Architectural Design

Goals:

1. Present results of surveying biomedical applications and defining a compositional set of elemental resources and operations. Present initial power and control strategies for the reconfigurable microliquid handling system architecture.
2. Present simulation of target biomedical applications using process flow simulation technology. Present baseline of reconfigurable microliquid handling system architecture and illustrate operation via architectural simulation
3. Present final design of reconfigurable microliquid handling system architecture.

Results:

See discussion under Tasks 1.1.1. and 1.1.2. Results from this task are reported in the theses of J. Jopling and T. Zhang.

- Task 2.2 Modeling and Simulation

Goals:

1. Present survey of process flow and performance simulation and applicable commercial offerings. Show a comparative process flow simulation of biomedical processes.
2. Show base-line process flow and performance simulation environment. Present initial biomedical application and architectural simulation models.
3. Show final process flow and performance simulation environment.

Results:

This task was focused on identifying the general biomedical application set and the specific applications to be used by MONARCH as well as architectural design and analysis. MONARCH V1.0 was conceived in Fall 1998 after an initial, cursory survey of a wide range of candidate applications for the architecture. This work would lead to a foundation of knowledge on which to build the simulation of applications executed on a given architecture. This, in turn, motivated a study of such simulation, specifically the Sabre Simulator and the corresponding MAST modeling language. Finally, this knowledge would also provide a basis by which to decide which applications and analyses may be implemented in a microfluidic architecture.

Work on the task investigated the further analysis of the equations of MEFS systems and simulation engines. A first version of DAENS (Differential and Algebraic Network Solver) was completed in MATLAB in the second quarter 2000. Detailed simulations of the washing/filling procedure were accomplished, with some expected and some interesting results. (see Appendix 1). From these results, a new model for washing/filling was devised that was more appropriate to representing the function. A second version of DAENS was then developed that allowed full simulation of a uTAS chip. Improvements included a new formulation/derivation of the numerical approach to solving the system. This appeared to be a more robust approach, and was included in a rough form in the network solver. DAENS was able to address simulation issues such as stiffness, vectorization, abstract data propagation, simultaneous simulation of all domains, and scaling.

Additional efforts included studying the low-level, detailed simulations of cornerstone microfluidic operations and further advancing the DAE network solver capability. This included extending the washing/filling simulation to study reaction kinetics in a

convective/diffusive mixing chamber. In addition, once the next few key features of the DAE network solver were in place, simulation of a real, existing MEFS system would be performed. Data/specs were acquired in order to accurately define the device and compare simulation results with those observed experimentally. Close collaboration with Dr. Donald Rose in Computer Science at Duke University was essential.

This work laid the basis and defined the need for a true composite domain simulator in microfluidics. Such a tool would require a model language structure that inherently supports multiple domains, and which supports both temporal derivatives and spatial derivatives/ discretizations. A simulation system would be also required that had algorithm stability, speed, and which runs algorithms that address multiple domain issues. Our new simulation environment was implemented in MATLAB, which meets the above requirements. Our new simulation system, unlike SPICE, naturally extends to system simulation in multiple domains.

The theory behind transforming arbitrary 'networks' of equations into a minimized state equation was researched, and assembled into the first version of the State-Space System Simulator (SSSS). This version is capable of transforming a (nearly) arbitrary linear network into the corresponding state representation, once provided categorical information about the branch-constitutive equations. This is the cornerstone algorithm needed to accomplish the state transformation and will be used as the 'kernel' of SSSS. Given the linear nature of the sample systems and the 'kernel', the resultant representation can quite efficiently be simulated with the built in MATLAB state-space tools. These built-in tools are limited to linear systems, however, and cannot be directly applied to a nonlinear network. Techniques for adding 'wrappers' to the kernel that extend the capability to nonlinear networks, as well as more arbitrary components, have been considered, and the foundation laid for these wrappers. Due to the end of MONARCH funding, work allowing a complete implementation of the first of these wrappers for state-based solution of nonlinear networks was discontinued.

Last quarter saw the results of implementing a state transformation algorithm in the linear two-terminal case. While relatively trivial in its application, the modular tools implemented in this simple case were reused in the implementation of the nonlinear case. In addition, the process of implementing the transformation reveals more intimate details about its function than equations can provide. Subsequently, the transformation was reanalyzed and re-derived for the nonlinear case. The solution was derived to completeness wholly analytically, which introduced certain insurmountable numerical issues. Primarily, this was due to the inability to properly represent/approximate a numerical solution that included the inverse function of an unknown system of equations. Upon rethinking the derivation, however, a solution was derived that is applicable to solution by numerical techniques. This was accomplished by stopping the analytical derivation earlier in the procedure at a point where the system was reduced to the simultaneous solution of an implicit nonlinear equation and a differential equation. Rather than continue analytically, each of these equations can be well handled by numerical methods if treated individually. The proposed solution approach for the generalized nonlinear two terminal case does exactly that.

Recently, the effort had begun to combine the tools from the linear case with the code necessary to implement the proposed solution method. Once the algorithm was in place, the simulation of test cases and the study/implementation of additional effects/features began.

Another aspect of Tasks 1.3 and 2.2 was the development of a model translator for SSSS that translates models in VHDL-AMS into the native format of SSSS. VHDL-AMS allows the designer to utilize a huge vocabulary and grammar to describe the behavior of a component or system in whatever way is easiest for them. SSSS, on the other hand, has very stringent data and format requirements for a model. It requires an equation describing the flux through each branch between nodes, and an equation for the potential across each node. Furthermore, it will require explicit declaration of the forms of these equations.

Work was continued last quarter on the intelligent model translator. In order for a hardware simulator to be useful, it must have models to simulate. The intelligent model translator was designed to translate general VHDL-AMS models to the format required by the SSSS, so they can eventually be simulated. The SSSS requires its own model format. Thus, in order to thoroughly test and experiment with various aspects of the simulator with models from different domains, existing AMS models must be leveraged.

The complexity of this model translator obviously depended on the types of differences in the model formats. If a source language contains the same information as the SSSS format, with merely a different syntax, this translation is trivial, effectively amounting to transcription. If, however, the translator will have to generate new information or change the form of existing information to generate the new model, it will have to contain some amount of intelligence and perform more difficult tasks. A quick look at the model formats shows that the latter is the case for translation from VHDL-AMS to the format required by SSSS. VHDL-AMS allows the designer to utilize a huge vocabulary and grammar to describe the behavior of a component or system in whatever way is easiest for them. SSSS, on the other hand, has very stringent data and format requirements for a model. It requires an equation describing the flux through each branch between nodes, and an equation for the potential at each node. Furthermore, it will require explicit declaration of the forms of these equations, so they must be implicitly understood by the program that generates them.

The last progress report identified an existing VHDL-AMS parser written for the JavaCC interpreter-generator. At the time, it could perform basic syntax checking by parsing a model and performing no actions other than reporting errors. Since then, this parser has been enhanced to identify key pieces of information in the source model that will be required for generating the SSSS model. The enhanced parser is able to generate appropriately named model templates in the SSSS format for each entity-architecture pair encountered. Furthermore, it performs all the necessary transcription of basic information. This basic information essentially consists of inputs to the model and initial or default values for these inputs and internal constants. The parser and input models

have been studied to identify the key challenges in generating the core of the SSSS model, namely the flux equations and jacobian.

Now that the basic translational components are in place, the more difficult information generation parts must be implemented. The key issues and challenges surrounding the generation of this information have been identified, and now must be explored. These issues comprise the real challenge of an intelligent model translator. When they are resolved, the translator will be able to generate a complete, usable SSSS model of a single component. The final step is to generalize the translator to generate whole systems of these components using existing behavioral and structural models as well as libraries.

Currently, the basic translational components are in place, and the more difficult information generation parts must be implemented. The key issues and challenges surrounding the generation of this information have been identified. These issues comprise the real challenge of an intelligent model translator. When they are resolved, the translator would have been able to generate a complete, usable SSSS model of a single component. The final step would have been to generalize the translator to generate whole systems of these components using existing behavioral and structural models as well as libraries.

Future Work:

Continuation of work on a composite domain simulator needs to be completed and extended to droplet-based systems with the following goals:

Task 2.2 goals for future work:

1. Study the effect/behavior of k-terminal devices on system matrix assembly and simulation. The rules for matrix formulation are key to an efficient simulator.
2. Perform demonstration and verification simulations with a new nonlinear method on simple 2-terminal nonlinear systems.
3. Complete assembly of the multiple domain simulator and perform detailed simulations of chosen reaction/detection chamber problems.
4. Produce a translator that can take models of different formats (starting with VHDL-AMS) and produce a model in the SSSS simulator's native format.

- Task 2.3 Pilot Fabrications

Goals:

1. Conduct pilot fabrication to assess and understand basic material properties and manufacturing procedures of proposed intelligent substrate structures.
2. Conduct pilot fabrication of initial layout of intelligent substrate, addressing system issues.
3. Conduct fabrication of final layouts and demonstration devices.

Results:

Numerous continuous flow and unit flow structures and test devices have been fabricated in this effort. We have successfully demonstrated that electrowetting technology is ready for implementation in advanced development applications.

4. TASK 3.0: MONARCH Technology Transition

Goals:

1. Work with industry and government to identify target biomedical applications having commercial potential and defense relevance.
2. Issue baseline design of the reconfigurable microliquid handling system architecture for review and comment.
3. Identify specific applications for MONARCH unit-flow technology and design tools in the commercial sector.

Results:

The following activities reflect our current progress in technology transition:

1. Completed a book contract with CRC Press to publish a Title entitled "Microfluidic System Simulation".
2. We have entered into initial discussions with the following companies regarding the transition of unit-flow technology to new product ideas: Becton Dickinson, Bio-Machines, Inc., StemCo Biomedical, Inc., LabNetics Inc., Vennworks, Nanolytics, Inc., CMA (Stockholm). We have also created a spin-off company called Fluometrics.
3. Four invention disclosures have been filed with Duke's Office of Science and Technology.

We have also published the following conference papers and journal articles:

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